Factors associated with sentinel lymph node status and prognostic role of completion lymph node dissection for thick melanoma

Title: Predictors of sentinel lymph node status and role of lymph node dissection in thick melanoma.

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Abstract

Introduction

Sentinel lymph node (SLN) biopsy is useful for the prognostic stratification of patients with thick melanoma. Identifying which variables are associated with SLN involvement and establishing risk in different subgroups of patients could be useful for guiding the indication of SLN biopsy. The value of complete lymph node dissection (CLND) in patients with a positive SLN biopsy is currently under debate.

Materials and methods

To identify factors associated with SLN involvement in thick melanoma we performed a multicentric retrospective cohort study involving 660 patients with thick melanoma who had undergone SLN biopsy. To analyze the role of CLND in thick melanoma patients with a positive SLN biopsy, we built a multivariate Cox proportional hazards model for melanoma-specific survival (MSS) and disease-free survival (DFS) and compared 217 patients who had undergone CLND with 44 who had not.

Results

The logistic regression analysis showed that age, histologic subtype, ulceration, microscopic satellitosis, and lymphovascular invasion were associated with nodal disease. The CHAID (Chi-squared Automatic Interaction Detection) decision tree showed ulceration to be the most

important predictor of lymphatic involvement. For nonulcerated melanomas, the histologic subtype lentigo maligna melanoma was associated with a low rate of SLN involvement (4.3%). No significant differences were observed for DFS and MSS between the CLND performed and not-performed groups. Nodal status on CLND was associated with differences in DFS and MSS rates.

Conclusion

We identified subgroups of thick melanoma patients with a low likelihood of SLN involvement. CLND does not offer survival benefit, but provides prognostic information.

Keywords: melanoma, sentinel lymph node biopsy, complete lymph node dissection, prognosis

Abbreviations

SLN: sentinel lymph node

CLND: complete lymph node dissection

SSM: superficial spreading melanoma

LMM: lentigo maligna melanoma

NM: nodular melanoma

ALM: acral lentiginous melanoma

CHAID: chi-squared automatic interaction detection

MSS: melanoma specific survival

DFS: disease-free survival

RR: relative risk

AHR: adjusted hazard ratio

Manuscript

1. Introduction.

Sentinel lymph node (SLN) biopsy is widely accepted as a staging method for intermediate-thickness melanoma (Breslow thickness, 1–4 mm). Its role in thick tumors (> 4 mm), however, remains controversial, because these tumors have a high risk of systemic dissemination, with occult systemic disease likely to be present in 10-20% of patients at the time of diagnosis [1]. Nevertheless, several studies have shown that SLN biopsy is useful in the prognostic stratification of patients with thick melanoma [2]. This, together with its value when selecting patients for new adjuvant treatments [3,4] means the procedure is still valid.

An SLN positivity rate of 5% is widely recognized as the threshold for the indication of SLN biopsy, since approximately 5% of patients who undergo this procedure will have a false negative test or develop one of the more common complications associated with the procedure, such as infection or seroma [5,6]. In cases of thick melanoma, with nodal involvement rates

around 35%, this yield is clearly exceeded [7,8]. Thick melanomas, however, display highly heterogeneous biological behavior [9], and a greater knowledge of the factors associated with SLN status in this setting could help to guide decisions regarding the indication for SLN biopsy.

After determining the presence of lymph node metastasis, the next step is to decide whether or not to perform complete lymph node dissection (CLND). The recent findings of the MSLT-II [10] and DECOG-SLT [11] trials showed that CLND did not increase melanoma-specific survival (MSS) compared with intensive ultrasound follow-up. However, both trials featured only a few cases of thick melanoma. Just 22.8% and 24% of the patients who underwent CLND in the MSLT-II and DECOG–SLT trials had melanomas thicker than 3.5 mm and 4 mm, respectively. There is some controversy thus about whether the conclusions of these two studies can be extrapolated to the setting of thick melanoma, where there is a higher risk of positive non-SLNs [12].

The aims of this study were to determine predictors of SLN positivity in thick melanoma and assess the role of CLND in these cases.

2. Material and Methods

2.1 Study Design

We conducted a multicenter, retrospective, observational study using prospectively collected data from patients with melanomas measuring over 4 mm in thickness (T4 according to AJCC) in whom SLN biopsy had been performed. Patients were recruited in five hospitals that form part

of the Sentinel Lymph Node Study Group in Melanoma (SENTIMEL). This group currently consists of 10 hospitals in Spain, Portugal, and Italy. For the current study we recruited patients from five tertiary hospitals, including four in Spain (Hospital Universitari Germans Trias i Pujol in Badalona, Barcelona; Hospital Clínic in Barcelona; Instituto Valenciano de Oncología in Valencia; and Hospital Universitario Virgen Macarena in Seville) and one in Italy (Dermatologic Clinic of the University Hospital "Città della Salute e della Scienza di Torino" in Turin). The data contained in the melanoma databases at the participating hospitals fully comply with strict ethical requirements and are regularly updated.

2.2 Study participants

Data were collected on all patients with melanomas measuring over 4 mm from the time at which SLN biopsy was introduced at each of the hospitals up to December 31, 2015. The procedure was introduced at different times in each hospital, with dates ranging from 1997 for Hospital Universitari Germans Trias i Pujol to 2004 for Hospital Universitario Virgen Macarena. The study was approved by the ethics committee at Hospital Universitari Germans Trias i Pujol.

2.3 Independent variables

The following clinical and histologic characteristics were selected as independent variables:

Demographic and clinical factors: sex, age, and anatomic location (head and neck, extremities, trunk, hand/foot, other).

Histologic factors: histologic subtype (superficial spreading melanoma [SSM], lentigo maligna melanoma [LMM], nodular melanoma [NM], acral lentiginous melanoma [ALM], and other histologic subtype), Breslow thickness, ulceration (present, absent), regression (present, absent),

microsatellitosis (present, absent), lymphovascular invasion (present, absent), CLND (performed, not performed), and nodal status on CLND (negative, positive).

2.4 Statistical analysis

For the first phase of the study, variables were classified as categorical (sex, histologic subtypes, ulceration, regression, microsatellitosis, lymphovascular invasion) or quantitative (age, Breslow thickness). The response variable was SLN positivity. In the logistic regression analysis, we first analyzed the association between SLN positivity and the study variables using univariate regression analysis. All variables significantly associated with SLN positivity in the univariate analysis ($p < 0.1$) were included in a binomial logistic regression model to adjust for confounders. We also applied the CHAID (Chi-squared Automatic Interaction Detection) decision tree method, which is a statistical technique that builds classification trees where each nonterminal node identifies a split condition, thereby producing optimal prediction of the response variable.

To analyze the role of CLND in thick melanoma, we built survival models for melanoma specific survival (MSS) and disease-free survival (DFS), calculated as the time from excision of the primary tumor to the event. Patients without an event were censored at the time of their last follow-up visit. The Kaplan-Meier estimator was used to construct nonparametric survival curves and the log rank test to compare curves between CLND performed and not performed and nodal positivity and negativity on CLND. Univariate Cox regression models were used to determine the association between positive or negative nodal status on CLND and survival. To analyze the potential effect of other factors, variables significantly associated with survival ($p < 0.2$) in the

univariate analysis were included alongside CLND in a multivariate Cox regression model to adjust for possible confounders.

2.4.1 Missing values analysis

Under the assumption that missing data were missing at random, 10 complete datasets were generated using multivariate imputation. The procedure included all variables that were to be subsequently analyzed, in addition to any variables that could help to explain the missing data. Each of 10 imputed datasets was analyzed using Cox regression to fit the model of interest to the outcome variables (DFS, MSS). Finally, the results of the complete datasets were combined into a single set of estimates using Rubin rules [13].

SPSS software was used for statistical analyses (version 20.0, Illinois, Inc; USA).

3. Results

3.1 Participants

A total of 660 patients who underwent SLN biopsy at the five study hospitals were included. The SLN was identified in 648 patients (98.18%), of whom 288 (44.4%) were women. The mean age of the participants was 58.2 years (interquartile range, 48–70). Metastatic involvement of the SLN was observed in 288 patients (44.4%). Table 1 shows the clinical and histologic characteristics of the study population stratified by SLN status.

3.2 SLN status

The logistic regression analysis showed that younger age, histologic subtype, ulceration, microscopic satellitosis, and lymphovascular invasion were independently associated with metastatic involvement of the SLN (Table 2).

3.3 Classification tree

Of the five variables significantly associated with SLN positivity, four (age, histologic subtype, ulceration, and lymphovascular invasion) were used in the CHAID tree (Fig. 1). Ulceration was the most important predictor of SLN involvement. For ulcerated melanomas, an age below 76 years and lymphovascular invasion increased the relative risk (RR) of SLN involvement (RR, 50.9; 95% CI: 10.5–247.7). In the case of nonulcerated melanomas, young age and three of the histologic subtypes—NM, SSM, and ALM—increased the risk of SLN positivity (RR, 56.7; 95% CI: 10.3–309.6). LMM and other histologic subtypes, by contrast, were associated with a low rate of SLN involvement (4.3%).

3.4 CLND vs. observation

Information on whether or not CLND was performed was available for 261 (90.6%) of the 288 patients with a positive SLN biopsy. The procedure was performed in 217 of the cases (83.14%). No significant differences were observed for 5- or 10-year DFS or MSS rates between patients in the CLND performed and not performed groups. The respective 5- and 10-year DFS rates were 34.7% (95% CI: 31.8–38.4) and 29.2% (95% CI: 25.5–32.9) in the CLND group versus 39.9% (95% CI: 31.8–48) and 33.3% (95% CI: 24.2–42.4) ($p = 0.5067$) in the non-CLND group (Fig. 2a). The corresponding 5- and 10-year MSS rates were 55.4% (95% CI: 51.5–59.3) and 42.9%

(95% CI, 38–47.8) in the CLND group and 62.7% (95% CI: 53.7-71.7) and 41.1% (95% CI: 28.7–53.5) in the non-CLND group (p = 0.7779) (Fig. 2b).

3.5 Nodal status on CLND

Positive nodes were observed on CLND in 69 (32%) of the 217 patients who underwent the procedure. CLND results were associated with differences in DFS and MSS rates. The DFS rates at 5 and 10 years were 41.5% (95% CI: 37.1–45.9) and 32.9% (95% CI: 28-37.8) for patients with negative nodes on CLND compared with 21.3% (95% CI: 16–26.6) and 21.3% (95% CI: 16–26.6) (p = 0.0003) for those with positive nodes (Fig. 2c). The corresponding MSS rates were 64.1% (95% CI: 60–68.2) and 52.4% (95% CI: 46.5–58.3) for patients with negative nodes on CLND and 37.5% (95% CI: 30.9–44.1) and 26.9% (95% CI: 19.8–34) (p = 0.0003) for those with positive nodes (Fig. 2d).

After controlling for confounders, nodal status on CLND retained its significance as an independent predictor of both DFS (adjusted hazard ratio [AHR], 2.25; 95% CI: 1.51–3.56; p < 0.001) and MSS (AHR, 2.2; 95% CI: 1.4–3.4; p < 0.001) in the multivariate analysis. Patient age at the time of melanoma diagnosis was also an independent predictor of DFS and MSS (Table 3).

4. Discussion

Considering that SLN biopsy has proven prognostic value in thick melanoma, it is important to identify which factors are most likely to predict SLN involvement, as this will help guide decisions regarding the indication for SLN biopsy on a case-by-case basis.

We have described a series of 660 patients with thick melanoma who underwent SLN biopsy. To our knowledge, this is the largest such study to date. We found that ulceration of the primary tumor was the most important predictor of SLN involvement. The role of ulceration as a predictor of lymph node involvement in thick melanoma has already been established in several studies [14-16]. In our series, SLN biopsy was positive in 48.7% of patients with an ulcerated primary tumor compared with 36.5% of those without ulceration ($p = 0.04$).

Considering that Breslow thickness has been found to be the most important predictor of lymph node involvement in intermediate-thickness melanomas [17], the less relevant performance of this predictor in our series of thick melanomas is somewhat surprising. It would seem reasonable to assume that once a tumor has reached a depth of 4 mm, its access to the lymphatic vessels will be guaranteed and whether or not it invades these will be determined by other factors.

Although thick melanomas have been classically considered to carry a high risk of metastasis to the regional lymph nodes, in our study they showed heterogeneous behavior. The risk of SLN involvement exceeded 50% in some cases (ulcerated melanomas in patients < 76 years with lymphovascular invasion and nonulcerated melanomas in patients < 36.5 years with NM, SSM, or ALM), while in others it was lower than 5%. In a subgroup of patients with nonulcerated LMM or other uncommon histologic subtype, for example, the risk of SLN involvement was just 4.3%. Probably this subgroup of other histological variants include cases of thick desmoplastic melanoma, a histological subtype with a proven low tendency to lymph node dissemination and where the indication of sentinel lymph node biopsy is controversial [18]. Our results confirm that

the decision to perform SLN biopsy in these patients with a yield of less than 5% must be carefully weighed up.

One finding from our study that is difficult to explain is that microsatellitosis, classically considered a risk factor for SLN metastasis [19], was more common in patients with a negative SLN biopsy. Information on microsatellitosis, however, was missing for almost half of the patients and the most likely explanation for this unexpected finding thus is a nonuniform distribution of missing data. Another limitation of our study is that we did not include mitotic index, although it should be noted that the usefulness of this predictor for assessing SLN involvement in thick melanoma has not been consistent [14-15].

Based on the results of the MSLT-II [10] and DECOG-SLT [11] trials, which failed to find a survival benefit for CLND versus intensive follow-up with ultrasound monitoring, CLND is no longer considered mandatory in patients with a positive SLN biopsy [20]. A survival benefit for MMS and even DFS was also absent in our series of patients with thick melanoma. It is, however, likely that in a period where CLND after a positive SLN biopsy was the standard of care, the patients who were not selected for CLND were patients with minimal lymph node tumor burden, and as such would have had a very low risk of non-SLN involvement.

There is no doubt that CLND has important prognostic value in terms of both MSS and DFS. The MSS rate at 10 years, for instance, was 53% in patients with negative nodes on CLND but just 26.9% in those with positive nodes. In our opinion, however, this prognostic value is not a strong enough argument to justify the use of a procedure with such high morbidity. Even in a

high-risk situation like ours (thick melanoma and SLN positivity), just 32% of patients had positive nodes on CLND. In other words, at least 68% of patients underwent unnecessary immediate CLND and were exposed to a high risk of lifelong morbidity. Madu et al. recently suggested that assessment of SLN tumor load, at least in patients with stage IIIA melanoma, could provide similar prognostic information to CLND, but without the associated morbidity risks [21]. Further studies are needed to validate these findings in patients with thick melanoma and SLN positivity (stages IIIC-IIID) [22]. Another important consideration is that the risk of relapse is high, regardless of nodal status on CLND. All patients should therefore be considered for adjuvant treatment and their management should not be based on the results of the CLND.

Another interesting finding in our study is the intriguing role of age in the behavior of thick melanoma. In the first part of our study we found that older patients had a lower rate of SLN involvement. Nonetheless, in patients with stage III melanoma, age was the only variable other than nodal status on CLND associated with poor prognosis, supporting reports from other studies of thin and intermediate-thickness tumors [23,24].

5. Conclusions

In conclusion, our identification of subgroups of patients with thick melanoma with distinct risks of metastatic SLN involvement should help to guide decisions on the indication for SLN biopsy. Our cohort, for example, included subgroups of patients who were very unlikely to have lymph node involvement. Our findings also indicate that CLND does not confer an MSS benefit in patients with thick melanoma and a positive SLN biopsy. Further studies, however, are needed to

validate these findings.

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Author Contributions:

Drs Boada, Tejera-Vaquerizo , had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Boada, Tejera-Vaquerizo. Acquisition, analysis, and interpretation of data: Boada, Tejera-Vaquerizo, Ribero, Puig, Nagore, Moreno-Ramírez. Drafting of the manuscript: Boada, Tejera-Vaquerizo. Critical revision of the manuscript for important intellectual content: Ribero, Puig, Moreno-Ramírez, Quaglino, Osella-Abate, Cassoni, Malvehy, Carrera, Pigem, Barreiro-

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Figure legends

Figure 1. CHAID (Chi-squared Automatic Interaction Detector) classification tree including the following variables: ulceration, histologic subtype, age, and lymphovascular invasion. RR indicates relative risk.

Figure 2. **(A-B) Estimated Disease-free, Melanoma-specific and Overall Survival according to study group.** Survival using the Kaplan-Meier method according to complete lymph node performed vs nonperformed (n=261). **(C,D) Estimated Disease-Free and Melanoma-Specific Survival according Complete lymph node dissection status.** Survival using the Kaplan-Meier method according to complete lymph node dissection status only for the group who underwent complete lymph node dissection (n=217).

Table 1. Characteristics of study population based on SLN status

	Negative SLN biopsy		Positive SLN biopsy			Whole series	
Variable	No.	% or IQR	No.	% or IQR	*p* value	No.	% or IQR
Sex (missing=0)							
Male	230	63.9%	176	61.1%	0.45	360	55.6
Female	130	36.1%	112	38.9%		288	44.4
Age at diagnosis (years) (cont.) (missing=0)	59.7	49-71	56.4	45-69	0.005	58.2	48-70
Anatomic location (missing=69)							
Head & neck	70	21.1	27	10.8	0.016	97	16.7
Extremities	82	24.8	63	25.2		145	25
Trunk	124	37.5	117	46.8		241	41.5
Hand/foot	51	15.4	40	16		91	15.7
Other	4	1.2	3	1.2		7	1.2
Breslow thickness (mm) (cont.)	6.66	5-8	7.12	5-8	0.152	6,86	5-8

Ulceration (missing=57)							
Absent	146	44.1	84	32.1	0.003	230	38.8
Present	185	55.9	178	77.9		363	61.2
Histologic subtypes (missing=9)							
LMM	15	4.2	4	1.4	0.005	19	3
SSM	79	22.1	86	30.3		165	25.7
NM	180	50.4	148	52.1		328	51.2
ALM	29	8.1	23	8.1		52	8.1
Other	54	15.1	23	8.1		77	12
Microsatellitosis (missing=301)							
Absent	181	89.6	141	95.9	0.029	322	92.3
Present	21	10.4	6	4.1		27	7.7
Vascular invasion (missing=320)							
Absent	156	86.2	100	71.9	0.002	181	56.6
Present	25	13.8	39	28.1		139	43.4
Regression (missing=180)							

Absent	233	86.9	176	87.1	0.952	409	87
Present	35	13.1	26	12.9		61	13

Abbreviations: ALM, acral lentiginous melanoma; Cont., continuous; IQR,interquartilic range; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.

Table 2. Univariate and multivariate analysis of prognostic factors of sentinel lymph node positivity

	Univariate analysis			Multivariate analysis		
Variable	OR	95% CI	*p* value	OR	95% CI	*p* value
Sex (missing=0)						
Male	1.12	0.86–1.52	0.47			
Female	Ref.					
Age at diagnosis (years) (cont.) (missing=0)	0.98	0.97–0.99	0.005	0.97	0.96–0.99	0.006
Site						
Head & neck	Ref.					
Extremities	1.84	1.08–3.2	0.029			
Trunk	2.26	1.35–3.77	0.002			
Hand/foot	1.88	1.03–3.43	0.038			
Others	2.64	1.09–6.38	0.03			

Breslow thickness (mm) (cont.)	1.03	0.99–1.07	0.1			
Ulceration						
Absent	Ref.			Ref.		
Present	1.58	1.13–2.21	0.01	1.71	1.01–2.94	0.04
Histologic subtypes						
LMM	Ref.			Ref.		
SSM	4.07	1.29–12.8	0.01	12.62	1.4–113.1	0.023
NM	3.07	1–9.37	0.05	13.58	1.5–121.9	0.02
ALM	3.09	0.9–10.49	0.07	9.1	0.96–86.8	0.06
Others	1.62	0.48–5.42	0.43	3.63	0.32–40.6	0.29
Microsatellitosis						
Absent	Ref.					
Present	0.36	0.14–0.93	0.034	0.32	0.11–0.9	0.031

Vascular invasion						
Absent	Ref.					
Present	1.61	0.99–2.62	0.012	3.48	1.71–7.03	0.001
Regression						
Absent	Ref.					
Present	1.01	0.59–1.75	0.95			

Abbreviations: ALM, acral lentiginous melanoma; CI, confidence interval; LMM, lentigo maligna melanoma: NM, nodular melanoma; OR, odds ratio; SSM, superficial spreading melanoma.

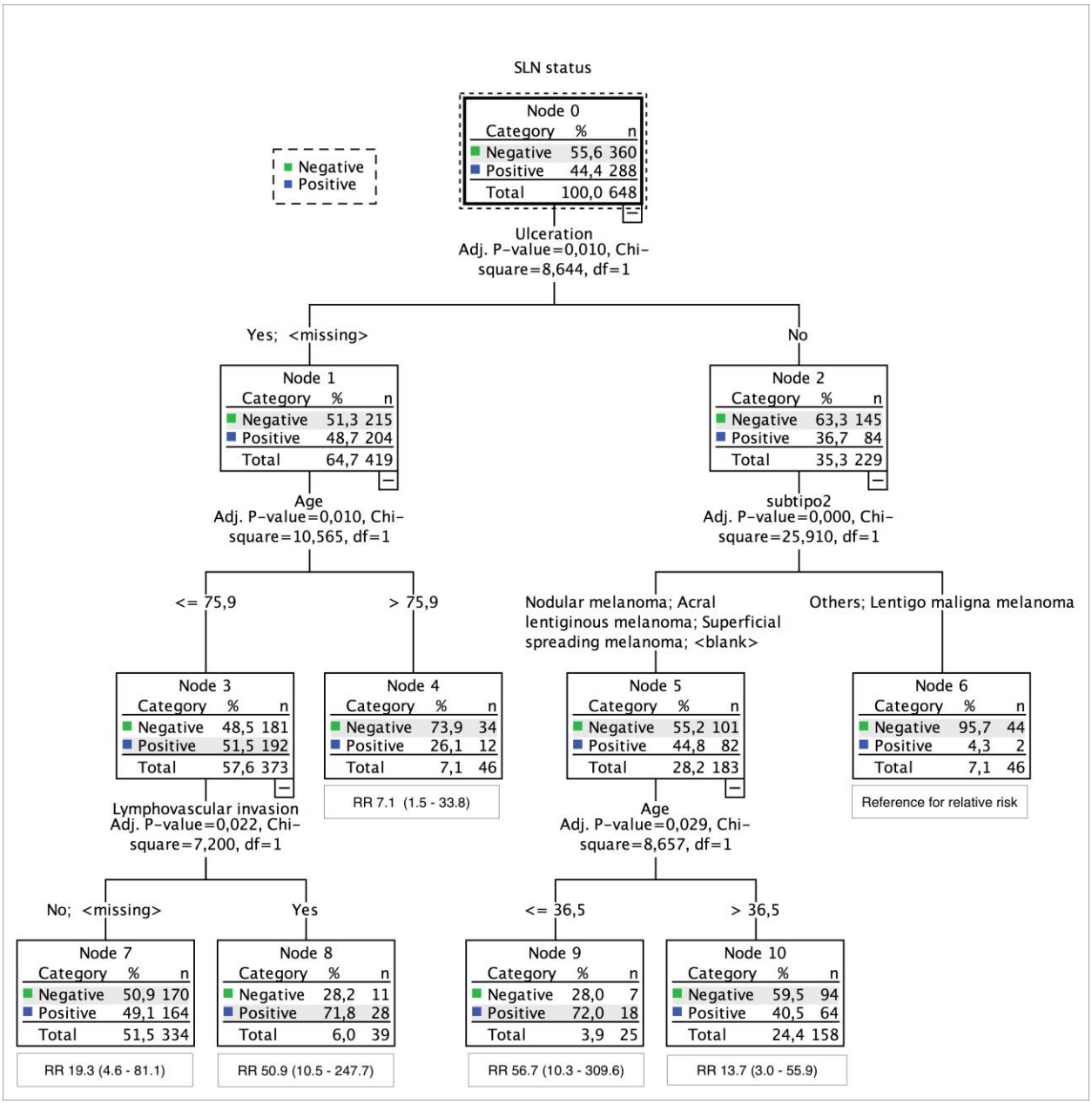
Table 3. Characteristics of study population based on complete lymph node dissection result (n=265)

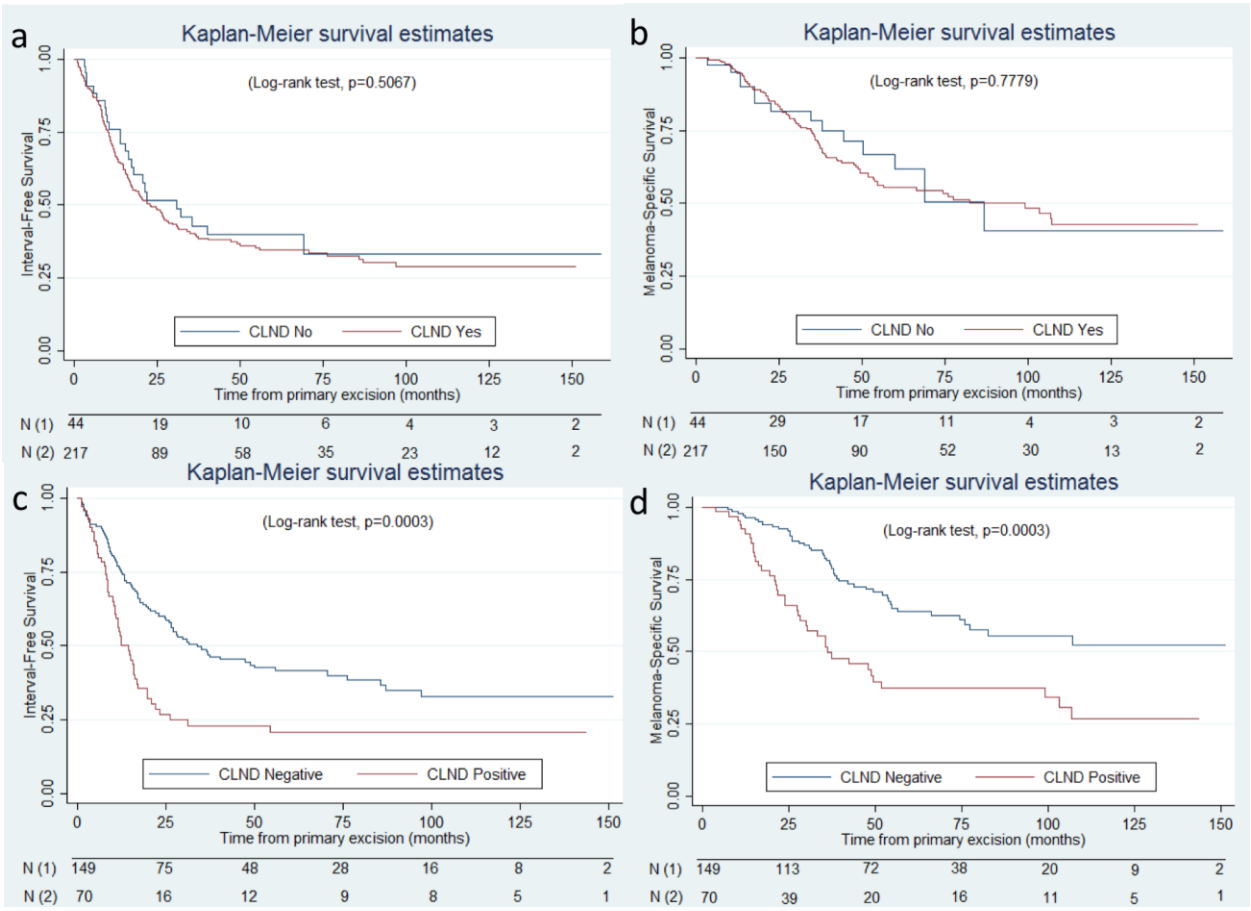
	Negative nodes on CLND		Positive nodes on CLDN			Whole series	
Variable	No.	% or IQR	No.	% or IQR	*p* value	No.	% or IQR
Sex (missing=0)							
Male	134	61.5%	84	61.1%	0.97	163	
Female	130	36.1%	112	38.5%		288	44.4
Age of diagnosis (years) (cont.) (missing=0)	59.7	49-71	56.4	45-69	0.005	58.2	48-70
Anatomic location (missing=69)							

Head & neck	70	21.1	27	10.8	0.016	97	16.7
Extremities	82	24.8	63	25.2		145	25
Trunk	124	37.5	117	46.8		241	41.5
Hand/foot	51	15.4	40	16		91	15.7
Others	4	1.2	3	1.2		7	1.2
Breslow thickness (mm) (Cont.)	6.66	5-8	7.12	5-8	0.152	6,86	5-8
Ulceration (missing=57)							
Absent	146	44.1	84	32.1	0.003	230	38.8
Present	185	55.9	178	77.9		363	61.2
Histologic subtypes (missing=9)							
LMM	15	4.2	4	1.4	0.005	19	3
SSM	79	22.1	86	30.3		165	25.7
NM	180	50.4	148	52.1		328	51.2
ALM	29	8.1	23	8.1		52	8.1
Others	54	15.1	23	8.1		77	12
Microsatellitosis (missing=301)							
Absent	181	89.6	141	95.9	0.029	322	92.3

Present	21	10.4	6	4.1		27	7.7
Vascular invasion (missing=320)							
Absent	156	86.2	100	71.9	0.002	181	56.6
Present	25	13.8	39	28.1		139	43.4
Regression (Missing=180)							
Absent	233	86.9	176	87.1	0.952	409	87
Present	35	13.1	26	12.9		61	13

ALM, acral lentiginous melanoma; CLND, Complete lymph node dissection; LMM, lentigo malignant melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.


SLN status
Negative
Positive
Node 0
Category % n
Negative 55,6 360
Positive 44,4 288
Total 100,0 648
Ulceration
Adj. P-value=0,010, Chi-square=8,644, df=1
Yes; <missing>
No
Node 1
Category % n
Negative 51,3 215
Positive 48,7 204
Total 64,7 419
Node 2
Category % n
Negative 63,3 145
Positive 36,7 84
Total 35,3 229
Age
Adj. P-value=0,010, Chi-square=10,565, df=1
subtipo2
Adj. P-value=0,000, Chi-square=25,910, df=1
<= 75,9
> 75,9
Nodular melanoma; Acral lentiginous melanoma; Superficial spreading melanoma; <blank>
Others; Lentigo maligna melanoma
Node 3
Category % n
Negative 48,5 181
Positive 51,5 192
Total 57,6 373
Node 4
Category % n
Negative 73,9 34
Positive 26,1 12
Total 7,1 46
Node 5
Category % n
Negative 55,2 101
Positive 44,8 82
Total 28,2 183
Node 6
Category % n
Negative 95,7 44
Positive 4,3 2
Total 7,1 46
RR 7.1 (1.5 - 33.8)
Reference for relative risk
Lymphovascular invasion
Adj. P-value=0,022, Chi-square=7,200, df=1
Age
Adj. P-value=0,029, Chi-square=8,657, df=1
No; <missing>
Yes
<= 36,5
> 36,5
Node 7
Category % n
Negative 50,9 170
Positive 49,1 164
Total 51,5 334
Node 8
Category % n
Negative 28,2 11
Positive 71,8 28
Total 6,0 39
Node 9
Category % n
Negative 28,0 7
Positive 72,0 18
Total 3,9 25
Node 10
Category % n
Negative 59,5 94
Positive 40,5 64
Total 24,4 158
RR 19.3 (4.6 - 81.1)
RR 50.9 (10.5 - 247.7)
RR 56.7 (10.3 - 309.6)
RR 13.7 (3.0 - 55.9)


a
Kaplan-Meier survival estimates
(Log-rank test, p=0.5067)
Interval-Free Survival
0.00
0.25
0.50
0.75
1.00
CLND No
CLND Yes
0
25
50
75
100
125
150
Time from primary excision (months)
N (1) 44 19 10 6 4 3 2
N (2) 217 89 58 35 23 12 2
b
Kaplan-Meier survival estimates
(Log-rank test, p=0.7779)
Melanoma-Specific Survival
0.00
0.25
0.50
0.75
1.00
CLND No
CLND Yes
0
25
50
75
100
125
150
Time from primary excision (months)
N (1) 44 29 17 11 4 3 2
N (2) 217 150 90 52 30 13 2
c
Kaplan-Meier survival estimates
(Log-rank test, p=0.0003)
Interval-Free Survival
0.00
0.25
0.50
0.75
1.00
CLND Negative
CLND Positive
0
25
50
75
100
125
150
Time from primary excision (months)
N (1) 149 75 48 28 16 8 2
N (2) 70 16 12 9 8 5 1
d
Kaplan-Meier survival estimates
(Log-rank test, p=0.0003)
Melanoma-Specific Survival
0.00
0.25
0.50
0.75
1.00
CLND Negative
CLND Positive
0
25
50
75
100
125
150
Time from primary excision (months)
N (1) 149 113 72 38 20 9 2
N (2) 70 39 20 16 11 5 1